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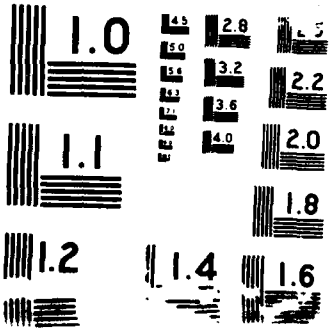
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SUMMARY REPORT

International Workshop on Monokines and Other Non-Lymphocytic Cytokines

December 6-10, 1987
Hilton Head, S.C.

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SUMMARY

Four hundred and seven academic, government and industrial scientists from nineteen countries attended the International Workshop on Monokines and Other Non-Lymphocytic Cytokines held at the Intercontinental Hotel, Hilton Head, SC, 6-10 December 1987. The fifty-three oral and 180 poster presentations dealt with the effects, mechanisms of action, physical properties, regulation and assay of many of the cytokines which affect the function of virtually every cell, tissue and organ system.

The keynote address was given by Jesse Roth (National Institute of Health) and served to set the tone of the meeting, i.e. in order to understand the function of an individual cytokine one must view it in the context of the whole organism's need to maintain itself, survive infection and repair injuries. Summaries of the current state of our knowledge of transforming growth factor beta, tumor necrosis factor, interferon beta2 and growth factors in hematopoiesis were given by Michael Sporn (National Cancer Institute), Grace Wong (Genentech), Alfons Billiau (Rega Institute, Belgium) and Malcolm Moore (Sloan Kettering) respectively.

Transforming growth factor beta (TGF beta), which can arise from activated lymphocytes, is a 25 kDa protein primarily platelet derived, which exhibits immunosuppressive effects (10^4 more active than cyclosporin), and angiogenic effects while promoting fibroblast matrix formation and facilitating wound healing. TGF beta is a powerful stimulant of fibroblast collagen and fibronectin mRNA and protein synthesis with effects persisting for up to 72 hours after exposure (J. Varga, Univ. Pa. Sch. Med. & Dent.). However, TGF beta also stimulates the secretion of PGE_2 to down regulate collagen synthesis (A. Diaz, Univ. Pa. Sch. Med.). TGF beta could be the primary mediator of anergy in the

severely injured patient. TGF beta appears to be able to selectively inhibit the growth of hematopoietic progenitor cells (F. Ruscetti, Lab. Mol. Immunoreg., NCI-FCRF). Whether this contributes to immunosuppression or can be reversed by interleukin-1 is unknown. TGF beta also appears to be involved in growth and development of various mesenchymal derived tissues; perhaps TGF beta functions to prevent an inappropriate immune response to antigens expressed by newly differentiated cells and tissues.

Interferon beta2 is known by numerous names, among them hybridoma growth factor, hepatocyte-stimulating factor and most recently interleukin-6 (IL-6). Interleukin-1 (IL-1) and tumor necrosis factor (TNF) can induce IL-6; IL-6 appears to be fibroblast-derived. Recombinant IL-6 can induce the synthesis of acute phase proteins by rat and human hepatocyte cultures (J. Gauldie, McMaster University, Ontario). IL-1 and IL-6 appear to have opposing effects on the synthesis of certain plasma proteins, e.g. IL-1 reduces fibrinogen synthesis while IL-6 promotes fibrinogen synthesis. IL-6 has been found in the plasma of burn patients. The opposing actions of IL-1 and IL-6 with regard to certain plasma proteins may explain why severely burned and severely burned-infected patients have significant differences in their plasma protein patterns which allow one to clearly distinguish between these two patient groups. Recombinant IL-6 has the ability to stimulate thymocyte proliferation as does IL-1, but IL-1 cannot promote hybridoma growth; IL-1 and IL-16 do not appear to exhibit sequence homology (M. Helle, Univ. Amsterdam).

The complex sequence of events which regulates hematopoiesis is only now faintly discernible. Hemopoietin-1 has been identified as IL-1 and even though IL-1 cannot elicit all of the stages of development of stem cells, it appears to act synergistically with granulocyte and granulocyte-macrophage colony stimulating

factors as well as colony stimulating factor-1 at various stages of hematopoiesis, as well as induce the colony stimulating factors in vivo.

There was a wealth of information about tumor necrosis factor (TNF) with regard to gene expression, synthesis and in vitro activities, yet the function of TNF in vivo, in terms of whole body economy, remains obscure. Though IL-1 and TNF have been reported to elicit identical arrays of physiological and metabolic activities, their mechanisms of action, the factors which control them and even their consequences to the host appear to be different. For example, though both IL-1 and TNF stimulate synovial cell plasminogen activator production, they appear to do so via different cell surface receptors (E. Mochan, Univ. Med. Dent. of NJ). Both TNF and IL-1 induce fever via the preoptic- anterior hypothalamus, yet the courses of fever are different (C.M. Blatteis, Univ. Tennessee). Both TNF and IL-1 appear to have antitumor activity in some model systems (S. Khadim, Univ. Western Ontario; S. Nakamura, Dainippon Pharm. Co.). Yet TNF has been implicated as the mediator of endotoxin-induced lethality (J.C. Mathison, Scripps Res. Inst.). In contrast IL-1 appears to provide mice with increased resistance to listeria and pseudomonas infections (C. Czuprynski, Univ. Wisconsin Sch. Vet. Med.; J.W.M. van der Meer, Tufts-New England Med. Ctr.). IL-1 and TNF are radioprotective and together have additive effects, while IL-1 and GM-CSF or G-CSF appear to be synergistic (R. Neta, Armed Forces Radiobiology Research Institute). IL-1 plus one of the colony stimulating factors thus may be useful in treating systemic mustard (HD) injury since mustard compounds have radiomimetic effects, especially with regard to bone marrow. In vitro, IL-1 alone or in combination with TNF causes pancreatic B cell cytotoxicity depending upon dose, duration of exposure and metabolic state of the cells (T. Mandrup-Paulsen, J.P. Palmer, Steno Memorial Hospital, Denmark).

With regard to expression of IL-1 and TNF, an inhibitor of protein kinase C blocks both IL-1 and TNF mRNA expression in endotoxin stimulated murine macrophages, while an inhibitor of the calcium/calmodulin kinase only blocks mRNA expression of IL-1 (E. Kovacs, Loyola Univ.). Arachidonate metabolites also have differential effects, decreasing TNF mRNA but not IL-1 mRNA production (S. Kunkel, Univ. Michigan Med. School). Cyclic AMP and cyclic AMP analogues can inhibit endotoxin stimulated TNF mRNA expression; gamma interferon potentiated the effects of low levels of endotoxin and blocked the inhibitory activity of exogenous cyclic AMP (S. Taffet, SUNY Health Sc. Ctr., Syracuse).

Considerable new information was presented concerning the local and systemic effects of cytokines, especially IL-1, as well as interaction amongst cytokines. Human recombinant IL-1 significantly reduces both serum T_4 and TSH levels in rats (J.M. Dayer, University Hospital, Geneva). Such reductions in T_4 and TSH are commonly found in severely ill and febrile patients. IL-1 cannot only cause changes in vascular permeability associated with acute inflammation (G. Habicht, SUNY at Stony Brook), it also can induce a chronic granulomatous response when implanted subcutaneously in a slow release polymer (C.J. Dunn, The Upjohn Company). IL-1 and TNF act synergistically on human osteoblast-like cells to induce proliferation and prostaglandin synthesis (M. Gowen, Sheffield Univ. Med. Sch., UK). Both IL-1 and TNF can induce pulmonary vascular injury in rabbits (S.E. Goldblum, Univ. Kentucky). IL-1 and TNF can act synergistically to produce physiologic and hematologic changes characteristic of shock (S. Okusawa, Tufts Univ. -New England Med. Ctr.). TNF alpha and interferon gamma appear to have opposite, perhaps antagonistic, effects on the development of seemingly inappropriate immune responses, e.g. immune

complex glomerulonephritis, in vivo but both depressed the antibody response to a T cell dependent antigen, if given before the antigen (C.O. Jacob, Stanford Univ.).

One of the difficulties in elucidating the roles of cytokines in sickness and in health is related to the precise measurement of active molecules at the site of action. Thus a number of papers dealt with the measurement of IL-1 in biological fluids and inflamed tissue by RIA (J. Cannon, G. Lonnemann, Tufts Univ.- New Engl. Med. Ctr.), by ELISA (C.-W. Chu, Cistron Biotechnology), and by immunocytochemistry (J. Jandinski, Univ. Med. & Dent., NJ). RIAs for TNF (A. Renter, Belgium and J.W.M. van der Meer, Tufts Univ.- New Engl. Med. Ctr.), a flurometric ELISA for TGF beta (B.S. Leung, Univ. Minn.) and an enzyme immunoassay for platelet derived growth factor (R.K. Kumar, Nat. Inst. Environ. Health Sci.) were described.

In vitro studies of the potential physiologic and pharmacologic regulation of IL-1 and IL-1 receptor production provided some insight as to how the body may regulate this cytokine and some indication as to how clinical conditions involving this cytokine may be treated. A neurokinin, substance P, responsible for the transmission of pain, can induce IL-1 production in a macrophage cell line (E.S. Kimball, McNeil Pharm.) while beta endorphin, an endogenous opiod, inhibits IL-1 release from stimulated blood mononuclear cells (C.F. Brummitt, Hennepin County Med. Ctr.). Glucocorticoid hormones can both reduce IL-1 and IL-1 mRNA production by monocytes (P.R. Young, Smith Kline and French Lab.) and increase IL-1 receptor number on fibroblasts (T. Akahoshi, National Cancer Institute, Frederick). There also appear to be differences in the number and affinity of IL-1 receptors on B cell versus T cell lines (R. Horuk, E.I. duPont de Nemours); perhaps the number and affinity of these receptors could be altered to affect the development of humoral and cellular immunity. A synthetic nonapeptide corresponding to the fragment 163-171 of human IL-1 beta appears to

have antitumor activity (T. Musso, Univ. Turin, Italy). It may be possible to use a variety of fragments of the various cytokines to selectively alter the metabolic, physiologic and immunologic status of animals and man.

Though the conference did not succeed in providing an explanation as to why there are so many cytokines, many of which have similar or at least overlapping activities, such as the array of colony stimulating factors. It is clear that these cytokines have survival value to the organism since they have been highly conserved, e.g. evidence was presented that IL-1 alpha and IL-1 beta have a common evolutionary ancestor (D. Chaplin, Washington Univ. Sch. Med.), yet both are still capable of being produced, depending upon cell type, nature of stimulus and presence of antagonists. This diversity of cytokines may simply reflect the diversity of cells which make up man and beast, or it may be necessary to allow an ordered interaction of cells and tissues regulating development, growth, identity and function of each cell and organ.

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